Stepping source prostate brachytherapy: From target definition to dose delivery
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Chapter 7
General discussion and future directions
This thesis describes several aspects of stepping source prostate brachytherapy. First, the benefit of MRI-based treatment planning is demonstrated in chapter 2. Then the stability of the implant configuration, patient anatomy and dose distribution during the 48 hour treatment is evaluated in chapters 3 and 4. Lastly, two newly developed tools for treatment planning and optimization are presented and compared to other optimization methods in chapters 5 and 6. This chapter starts with a general discussion on the studies presented in chapters 2 – 6, divided into three sections: Imaging (7.1), Implant stability (7.2) and treatment plan optimization (7.3). In the second part of this chapter (7.4), (technical) developments and future directions that are linked to the subjects described in chapters 2-6 are discussed.

7.1 Imaging and target volume definition

MRI- versus CT-based treatment planning (chapter 2)
The aim of chapter 2 was to establish the benefit of using MRI-based delineation and treatment planning. Often, a CT scan is acquired after implantation for the delineation of the prostate and organs at risk (OARs). However, prostate boundaries are difficult to distinguish on CT, especially at the interface between bladder and at the posterior base. The lack of soft tissue contrast leads to large uncertainty in determining the prostate volume. Due to these uncertainties, large variations are observed between observers or even within different observers [1-3].

Due to its better soft tissue contrast, most efforts to decrease delineation uncertainty involve the implementation of MRI, because the MRI-based delineated target volume is more representative of the actual prostate volume than the CT-based volume [1,4,5]. Not all institutes have direct and unlimited access to an MR scanner, but frequent evaluation of pelvic MR images will be useful in the delineation of the prostate on CT. The addition of MRI reduces the contouring variability found when CT images are used [6,7].

It must be noted that also with MRI-based target contouring, variability is found between different observers [8,9]. So obtaining the correct target volume for treatment planning is not guaranteed. Part of the interobserver variability on MRI results from lack of knowledge or consensus, and can be reduced with education [10]. This is also the case for CT, but though education can help in CT-based prostate delineation, some boundaries will remain hard to identify.

Several studies show that prostate volume is overestimated on CT [1,11]. This implies that smaller volumes can be treated when using MRI. However, in the study described in chapter 2, the volumes of CT- and MRI-based prostates were comparable. Unlike in external beam radiotherapy (EBRT), in brachytherapy the radiation oncologist is influenced by the implanted catheters. The tendency to delineate the implant (seeds or cath-
eters) rather than the actual prostate when using CT has been observed frequently [6,12-14]. Furthermore, the same person had already visualized the prostate with ultrasound during the implantation procedure. These factors have possibly contributed to a smaller volume on CT and therefore to the small absolute differences in measured volume.

We demonstrate that the basal part of the prostate is larger on MRI. When taking this into account during treatment planning, improved target coverage can be achieved. However, the values of the differences in prostate target coverage ($V_{100\%}$ and $D_{90\%}$) may be different for other observers and at other institutes. Besides prostate contouring, implantation and treatment planning at other institutes may differ from our clinical practice. Interobserver variability on MRI can be reduced with education [10], which is less the case for CT. Physicians can benefit from the addition of MRI in their own clinical practice to improve target definition [6,7]. To conclude, MRI-based treatment planning, or the addition of MRI, improves conformity and coverage of the actually intended target.

### 7.2 Anatomical variations and implant stability

Deviations due to anatomical variations (chapter 3)

Three CT-scans, originally acquired for the first 31 prostate cancer patients treated with pulsed-dose rate (PDR) brachytherapy at the AMC, form the basis of chapter 3 and 4: the regular planning CT and two repeat CTs, obtained 24 and 48 hours after the implantation.

An increase in rectum dose was observed on the repeat CTs, which was mainly caused by changes in rectal filling, visible on the CT scans. The increase in dose did not correlate to delineated rectum volume, but to the distance between prostate and rectal wall. Taking rectal motion into account during treatment planning by adding a margin or delineating a worst-case scenario can reduce the risk of overdosing the rectum but may compromise target coverage. When rectal dose is high, leading to severe rates of rectal toxicity, applying rectal spacers may be a better approach. Materials such as injectable hydrogel can be applied to increase spacing between rectal wall and prostate [15,16]. The resulting rectal dose reduction may decrease the risk of rectal complications, which could be of particular importance in salvage brachytherapy. Incidence of rectal complications in patients who have not received prior radiation, is relatively low for brachytherapy [17,18]. In previously irradiated patients however, the risk of bowel complications is significantly increased [19,20].

It is impossible to establish how much the dose was affected by each of the factors separately. Possible causes are catheter displacement, changes in the size and/or shape of the prostate, and changes in rectum and bladder position with respect to the prostate.
Furthermore, the CT scans only capture the patient and implant geometry at a given moment. Nevertheless, the changes observed in target coverage during treatment were limited, so dose to the prostate appeared to be stable throughout the treatment.

**Organ delineation**

Some remarks should be made on the findings presented in chapter 3. All measurements in this study depended on accurate (CT-based) delineations and catheter reconstructions. Delineation accuracy is limited by the lack of contrast on the CT scans (chapter 7.1). Furthermore, in brachytherapy, prostate contouring is often biased by available landmarks such as catheters (or seeds) and implanted markers [6,12-14] often resulting in an overestimation of dosimetric quality. This bias may have been present in this study as well. The markers that were implanted in these patients at the apex and base of the prostate may also have resulted in a false appearance of certainty. In chapter 4 we see that these markers have migrated over the course of treatment, especially after the first 24 hours. Therefore, one should be careful using them to indicate the outermost apical and outermost basal slice. The catheters may appear to have shifted relative to the prostate, when in fact the markers are shifted, resulting in an incorrect measure of change in target dose. Although an experienced physician reviewed all contours to minimize these problems, higher contrast images, preferably acquired using MRI, are needed to verify our findings.

**Prostate oedema and implant stability (chapter 4)**

In the study described in chapter 4, the same set of CT-scans was used to study prostate deformation. Catheter insertion causes trauma that could give rise to swelling of the gland [21,22]. Swelling of the prostate caused by oedema and the accompanying catheter displacement potentially decrease target coverage and conformity of the dose distribution. This is an important issue in the timing of dosimetry in low-dose rate (LDR) permanent brachytherapy. Prostate volume enlargements of 20% to even 50% have been reported [21,23-25]. The swelling develops in the first 24 hours after implantation after which it slowly resolves [21,25].

From the data presented in chapter 3, no conclusions can be drawn about changes in prostate volume during treatment, or about possible expansion of the prostate that could arise due to the trauma of catheter insertion. The delineations of the prostate by the physician did not show any volume changes during treatment. However, delineations are not sufficiently reliable to investigate deformation of the prostate gland during treatment. The available catheter positions are the best surrogate for prostate gland deformation. In chapter 4, we therefore attribute the change in the position of the catheters to deformations inside the prostate gland.

The analysis of catheter positions resulted in the majority of cases in an increase of implant diameter, although limited. Some individuals show a volumetric increase of
more than 10%. The apparent substantial increase of 10%, however, originates from small diameter changes (range -1 to 1.6 mm) and result in volume changes of a few cubic centimetres. Taking the 1 mm accuracy in catheter reconstruction into account, such volume changes can still be considered negligible.

**Drawbacks of registration methods**

The residual difference after matching the catheters was attributed to displacement. Displacement of the entire implant however, is corrected for by the matching procedure and therefore not detected as such. The catheters can exhibit caudal migration relative to the prostate gland. A possible explanation of this caudal displacement of catheters is the development of periprostatic oedema. This periprostatic oedema appears predominantly in the perineal region near the apex of the gland and is assumed to develop in 12–18 hours after implantation, so may play a role in the 48 hour PDR treatment. Unfortunately, the presence of periprostatic oedema is not detectable by analysing displacements of catheters, since these are located inside the prostate.

A marker-based registration of the catheter positions was applied to visualise entire implant displacements as well. Unfortunately, this match is less robust than the catheter-based registration, since only three markers were available. Furthermore, the markers appeared to display migration, since the distance between markers increased on average 0.6 mm between the first and last CT scan. This indicates that these markers are not sufficiently stable to use for reliable matching and hampered the evaluation of displacements of the entire implant.

**Concluding remarks on oedema**

From the resulting catheter displacements we established that there is limited effect of oedema between planning CT and delivery of treatment. It could be that any effect of oedema from catheter insertion took place in the time between implantation and the first scan, but this hypothesis cannot be confirmed with our data, since no CT-scan was acquired prior to the implantation procedure.

### 7.3 Treatment plan optimization

**EGO and IIP (chapter 5)**

Treatment planning for prostate brachytherapy is normally performed with graphical optimization or an automated inverse optimization method. The two most common commercially available automated methods are Inverse Planning Simulated Annealing (IPSA) [26] and Hybrid Inverse Planning and Optimization (HIPO) [27]. Some institutes start with geometrical optimization [28,29], followed by fine-tuning with graphical optimization. Two novel treatment planning methods, Enhanced Geometrical Optimization (EGO) and Inverse Interactive Planning (IIP) are presented in chapter 5. In this chapter,
these two methods were combined to demonstrate the feasibility of performing EGO, followed by IIP for stepping source prostate brachytherapy treatment planning. Below, the value of these methods will be discussed.

**EGO and dose homogeneity**

EGO was developed as an enhanced version of the traditional geometrical optimization [28,29], and offers a dose distribution that is as homogeneous as possible throughout the implanted volume. The goal of the traditional geometric optimization (GO) is to improve dose-homogeneity across the implanted volume, but it offers no opportunity to increase or decrease its flattening effect on the dose distribution, even though this is desirable in the case of an irregular implant to avoid cold- or hotspots. With EGO we aimed to improve the homogeneity as compared to other geometric optimization methods. A common index to measure the homogeneity is the dose homogeneity index defined as $$DHI = 1 - \frac{V_{150\%}}{V_{100\%}}$$ which is extracted from the target dose-volume histogram (DVH) [30]. EGO flattens the dose distribution by aiming at the same dose level in the areas midway between the catheters, but by doing that, increases the fraction of the target volume that receives 150% of the prescription dose, and decreases the fraction of the target volume with much higher doses. Applying EGO therefore does not improve the homogeneity index [30]. Other measures might better distinguish between different types of dose distributions. Such measures should have clinical relevance, but at present, not enough is known about the relationship between homogeneity of a dose distribution and clinical outcome.

**IIP, as alternative to graphical optimization**

After EGO, or an automatic inverse optimization method such as IPSA or HIPO, has created a dose distribution, manually fine-tuning the dose to adapt to patient specific requirements will usually be desired. IIP was developed to serve as a user-friendly alternative to graphical optimization, aiming at improving the ease of planning and reducing treatment planning duration. Graphical optimization, although widely used, is generally time consuming and requires considerable experience [31,32].

IIP maintains the benefits of graphical optimization, i.e. the user interaction and local control of the dose distribution, but instead of performing multiple drag-and-drop actions on the isodose lines, the highest or lowest dose to a ROI is adapted. The result is immediately visualized and evaluated by the user. This real-time user interaction is essential to quickly understand and visualize the available trade-offs. We therefore believe that IIP has added value in the daily clinical practice of (prostate) brachytherapy treatment planning, by making it possible for the physician to interact with the dose distribution and translate patient specific clinical goals to the dosimetry.

**IIP, as alternative to other algorithms**

With IIP, adaptation of the dose can be done locally when part of the dose distribution
is already satisfactory, while automatic inverse algorithms perform optimization of the entire dose distribution at once. Because this is a non-linear, multi-objective optimization problem, finding the optimal settings to obtain the most desirable dose distribution involves trial-and-error. A small improvement of one dosimetric index may result in a large deterioration of another dosimetric index, or vice versa. IIP immediately displays the values of these indices, which is useful when navigating through possible dose distributions. The strength of IIP is that the user can explore the trade-offs within the dose distribution for a given patient using real-time interaction, to understand the possibilities and impossibilities.

In addition, the highest dose to a ROI is directly related to the resulting DVH parameters, making steering towards the desired solution straightforward. In the latest version of IIP, not only lowest and highest doses can be adapted, but one can also enter a volume that should receive at least a certain dose, so the dose can be directly optimized on DVH parameters.

A comparison of inverse optimization algorithms (chapter 6)

Comparing different methods

Four treatment planning methods for PDR (or high-dose rate, HDR) prostate brachytherapy were compared (Table 1): Graphical Optimization (GrO), IPSA, HIPO and EGO-IIP. These methods were used to create treatment plans according to clinical standards. All methods were equally capable of creating high quality treatment plans. The study resulted in patient cases for which the dose distributions were different, even though the same level of compliance to clinical constraints was achieved. Because of the large number of scoring items that must be taken into account, comparing the performance of these optimization methods is not trivial. A compromise between target coverage and dose to the OARs has to be made. In terms of DVH parameters, especially the trade-off between prostate \(D_{90\%}\) and urethra \(D_{1\text{cm}^3}\) is clearly visible. Although most radiation oncologists also evaluate the dose distribution by assessing the isodose patterns, the isodose lines were not compared in this study. An expert opinion could be added to the analysis, for instance by rating the different plans from 1 to 4. The comparison of the four treatment planning methods was carried out in our clinical setting with specific DVH criteria. A multi-institutional study should be performed to determine the influence of applying different clinical standards.

Dose homogeneity

With the addition of EGO we aimed to improve the homogeneity of the dose distributions. No differences in homogeneity were found between the four methods. From the previous chapter we already know that EGO does not lower the \(V_{150\%}\). In addition, for IPSA and HIPO, a modulation restriction parameter was applied to limit large variations in dwell times, which may also have limited the difference between methods. Only for
very high doses, e.g. $V_{300\%}$, we observe smaller volumes with these high doses for EGO-IIP. Further analysis, using fixed values for $D_{90\%}$ and $V_{100\%}$, is needed to compare the dose homogeneity of the different methods. In addition, performing the optimization with and without applying the modulation parameters for IPSA and HIPO would demonstrate their effect. From the current data, no judgements can be made on this, since all IPSA and HIPO plans were created with modulation restriction. Others reported indeed a decrease in maximum dwell times from using the modulation restriction. In terms of DVH parameters, its effect was small, resulting in a slight overall decrease in dose [33,34].

**Dwell time analysis**

Holm et al. demonstrated that the linear penalties that are used in the objective functions of IPSA and HIPO give rise to dwell time patterns composed of a limited number of dwell positions [35]. When many dwell positions remain unused, relatively long dwell times arise for the remainder of dwell positions with nonzero dwell time. To smooth the distribution of dwell times over dwell positions, a dwell time deviation constraint was developed for IPSA and a dwell time gradient restriction for HIPO [33,34]. The use of this dwell time 'smoothing' has been reported in the literature to improve homogeneity, decrease hot-spots and increase plan robustness [36]. In chapter 6 it is shown

<table>
<thead>
<tr>
<th>Optimization Method</th>
<th>Abbreviated Name</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graphical Optimization</td>
<td>GrO</td>
<td>Manual method</td>
<td>Drag-and-drop of isodose lines</td>
</tr>
<tr>
<td>Inverse Planning Simulated Annealing</td>
<td>IPSA [26]</td>
<td>Automatic inverse method</td>
<td>Set class solution of minimum + maximum dose to surface and volume of ROIs, including the weight of each objective</td>
</tr>
<tr>
<td>Hybrid Inverse Planning and Optimization</td>
<td>HIPO [27]</td>
<td>Automatic inverse method</td>
<td>Set class solution of minimum + maximum dose to volume of ROIs, including the weight of each objective</td>
</tr>
<tr>
<td>Enhanced Geometrical Optimization – Interactive Inverse Planning</td>
<td>EGO-IIP (Chapter 5)</td>
<td>Two step method with manual interaction using IIP</td>
<td>Interactively set minimum and maximum dose to surface of ROIs</td>
</tr>
</tbody>
</table>
that despite the use of the dwell time deviation constraint for IPSA and HIPO, IPSA still results in solutions using the least number of dwell positions.

In brachytherapy, a treatment plan should be robust against uncertainties in location of dwell positions and catheter displacements [36]. However, no studies were found that test the hypothesis of linking dose homogeneity and homogeneity of dwell times to plan robustness. Currently, robustness evaluations are not available in brachytherapy treatment planning software and therefore not routinely performed for PDR and HDR.

7.4 Future directions

Imaging and image guided focal treatments

Multiparametric MRI

As mentioned, MRI is often adopted for improved target definition. Additional information on for instance the location of the dominant intraprostatic lesion or the presence of extracapsular extension can be retrieved from several image modalities. With multiparametric MRI a combination of anatomical and functional images is used to detect and locate such features [37]. In addition to the standard anatomical T2 weighted MRI, functional techniques are diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) imaging and magnetic resonance spectroscopy. Which combination of functional techniques to use, including image sequences and other specifications like the use of an endorectal or body coil, is not yet clear [38]. For instance, the combination of T2 and DWI is insufficiently sensitive for small foci and has limited specificity [39]. In general, multiparametric MRI has a higher sensitivity in higher risk prostate cancer lesions [40].

Focal therapy

Primary prostatic lesions can be defined using modern imaging techniques like multiparametric MRI, contrast-enhanced ultrasound (CEUS) and PET imaging. These imaging techniques are potentially applied in brachytherapy for sub-boosting of the dominant lesion, as demonstrated in treatment planning studies [41-46]. For instance, with contrast-enhanced ultrasound potentially a very high agreement with histology can be reached in the detection of intraprostatic lesions [47]. CEUS is easily integrated in the ultrasound-guided prostate implantation procedure. By using CEUS to localize the primary lesions, the dose distribution can be adapted to include a higher dose to these lesions [45].

These imaging techniques may be used to enhance tumour control while still relying on the treatment of the entire gland. Due to the multifocal character of prostate cancer, this is a relatively safe strategy, when doses to the OARs are kept low [48]. Future trials should demonstrate the clinical benefit of such image-guided dose escalation. A randomized trial in the Netherlands is set up to measure the benefit in biochemical control.
for an additional integrated focal microboost during EBRT [49].

Many techniques to deliver focal therapy exist [50]: brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU) [51, 52], electroporation [53], laser ablation [54, 55] and photodynamic therapy [53, 56]. Even though the reliability of the imaging techniques is still limited, experimental clinical studies are carried out to perform focal therapy, where the treatment is based on the primary lesion(s) instead of the entire gland [57-59]. Focal therapy is more appealing to men with clinically significant prostate cancer than active surveillance [60], although concerns have been raised on the overtreatment of low-risk prostate cancer [50]. Focal treatment potentially reduces damage to the surrounding normal tissue, such as external urinary sphincter, bladder neck, neuro-vascular bundles and rectal mucosa, thereby reducing complications as compared to whole gland treatments. Currently a feasibility trial is being performed in the Netherlands using MRI-guided focal HDR brachytherapy for localized prostate cancer, which aims to limit gastrointestinal and urogenital toxicity [61].

It is not clear whether the benefit of primary focal therapy over radical therapy can be demonstrated. Radiobiological modelling, including patient specific tumour biology and clinical data is needed to establish whether focal treatment results in non-inferior tumour control, as compared to whole gland treatments. Equally important is to improve current imaging techniques and their correlation to histopathology.

A likely endpoint in clinical trials is toxicity, but quality of life after treatment and costs of treatment plus follow-up also play a large role. Also recurrences and the availability of subsequent treatment options are important issues. Taking all parameters into account, to answer these questions and to establish an improvement or even non-inferiority in a (randomized) trial is a challenge [62]. A first step to establish the role of prostate brachytherapy in focal therapy is undertaken at Memorial Sloan-Kettering Cancer Center with a non-randomized phase II study with the tolerance profile of focal brachytherapy as primary endpoint [59].

Implant stability: Deformations and dose delivery
Two chapters (3 and 4) discuss possible deformations during the PDR brachytherapy treatment. There are different options to deal with resulting variations or decrease uncertainties in the delivered dose. For instance, to avoid unnecessary patient transportation, mobile imaging modalities such as TRUS or in-room cone-beam CT are adopted [63]. The uncertainty in delivered versus planned dose can also be minimized when the dose is given in a single high dose fraction [64]. HDR is characterized by short treatment times when a high dose is given in a single fraction [65, 66]. Time and cost-efficiency of HDR can be improved by reducing the number of fractions to an ultra-hypofractionated schedule. The remainder of this section is used to discuss developments in hypofractionated treatments, delivered by HDR brachytherapy or external beam modalities.
Hypofractionation with HDR brachytherapy

Some uncertainties exist in the underlying radiobiology of prostate cancer. Theoretical radiobiological effects influence the potential differences between PDR and HDR and the choice of (hypo-)fractionation schedule. Due to the apparent low $\alpha/\beta$ value of the prostate, interest in hypofractionated treatments is growing and the first clinical data from HDR as monotherapy are becoming available [67-73]. A high biological effective dose can be achieved inside the prostate, which appears to be confirmed by the first clinical results on local control. Potential extra-capsular extension is usually not treated with brachytherapy when given as monotherapy, but in a recent publication on HDR as monotherapy the PTV was extended to cover extra-capsular disease, so this perspective may change in the future [70]. The high doses decrease the opportunity for normal tissue repair and therefore increase the risk of late urinary complaints [74]. Thus far, the short duration of the treatment and especially the dose conformity appear to keep toxicity low, but follow-up is relatively short.

To demonstrate long-term safety and efficacy of hypofractionation in the primary treatment of prostate cancer, longer follow-up is needed. The safety compared with standard fractionation should be established, as well as non-inferiority for clinical effectiveness. Extreme hypofractionation may have greater toxicity and therefore requires reporting of randomized data prior to application outside of a clinical protocol [75].

Hypofractionation with alternative treatment modalities: SBRT and proton therapy

External irradiation techniques like stereotactic body radiotherapy (SBRT) and proton therapy are increasingly competing with temporary implant brachytherapy as a (hypofractionated) treatment for prostate cancer.

With standard SBRT using a standard linear accelerator, 30-40 Gy is delivered ultra-hypofractionated in 4 or 5 fractions. A special modality for stereotactic radiotherapy is image-guided robotic radiosurgery, e.g. the Cyberknife unit, in which gold fiducial markers are used for real-time tumour tracking. With the Cyberknife, the dose distribution of HDR brachytherapy can partly be reproduced [76]. However, brachytherapy is characterized by very high doses near the catheters and superior dose gradients outside the target. Lastly, with brachytherapy the total patient volume receiving a low dose is relatively small. Non-robotic SBRT is more readily applicable than Cyberknife treatments, but intrafractional motion has to be taken into account and appropriate margins need to be applied [77,78].

With modern proton therapy, using pencil beam scanning delivery, highly conformal dose distributions can be obtained, due to the physical properties of protons. Protons exhibit limited scatter and penetrate the body to a finite depth based on the energy of the beam. However, due to the steep gradients in the dose distribution, it is highly sensitive to uncertainties along the beam path (range uncertainties) and organ position.
These uncertainties can affect target coverage significantly, and cause unnecessary dose to OARs [79]. Performing robust optimization can minimize the influence of potential perturbations in the dose distribution. Usually one needs to find a balance in trading conformity for robustness against these uncertainties [80].

Although results from prospective studies are promising [81,82], no clinical benefit for prostate cancer with proton beam therapy as compared to photon beam therapy has been established thus far [83,84]. Future data on 3D image guided proton therapy using pencil beam delivery will show whether proton therapy can be improved both in clinical and in cost efficiency.

Even with the latest delivery techniques and robust treatment planning, image guidance is much more important with external irradiation than with brachytherapy. With brachytherapy there is less concern on tumour motion, as the implant will move together with the prostate [85,86]. Target coverage is maintained throughout the entire treatment, provided that no significant catheter displacements occur (chapters 3 and 4). In addition, the high costs involved in proton therapy are likely to result in better cost-effectiveness for brachytherapy. Finally, of all modalities stepping source brachytherapy still creates the most conformal dose distribution [87-91].

Treatment plan optimization

Future directions for EGO
In this thesis, EGO is applied to prostate cases, after which IIP is used for subsequent dose shaping. In implant configurations with peripheral catheter placement, the effect of EGO will be limited. Catheters in a prostate implant are often placed non-uniformly or peripherally. Such implants may not always be ideal for geometrical optimization. The subsequent use of IIP will always reduce the ‘flattening’ of the dose distribution.

Further evaluations are needed to quantify the gain that can be achieved with EGO. Institutes where the traditional geometrical optimization is extensively used will benefit from EGO. To improve EGO, it should be tested at different institutes to establish the added value for the different implant geometries, including the number of catheters used.

Instead of for prostate implants, EGO is perhaps even more useful for template-based implants. It should therefore be evaluated for other brachytherapy applications as well, like breast, floor of mouth or other head and neck implants.

Future directions for IIP
The real-time interactive nature of IIP is suitable for shaping the dose distribution. The optimality of a solution might not be essential. What is more important is the possibility for the treatment planner to easily and quickly obtain and visualize suggested
dose distributions that are equally compliant to the constraints, as is done with IIP. The suggested solutions then reveal the trade-offs between the different conflicting objectives, which the user can choose from. IIP has to be tested at more institutions and for other treatment sites to firmly establish its role in brachytherapy treatment planning. Further research is needed to improve the ease of planning with EGO-IIP. Furthermore, IIP-protocols should be developed to decrease the user dependence.

Within IIP, the user has the option to optimize directly on dose-volume parameters. This was not yet included in the methodology of chapters 5 and 6, but this has great potential due to the direct correspondence between input- and clinical output parameters. Future work is needed to test the updated version of IIP in which direct DVH-parameter optimization is possible.

In IIP, the conversion of dose to the common radiobiological equivalent of dose \( (\text{EQD}_2) \), is also implemented, which allows for optimization directly on \( \text{EQD}_2 \) values. Conversion of physical doses to \( \text{EQD}_2 \) values will ease the comparison between institutes with different fractionation schedules and different DVH criteria. This will improve objectivity when comparing treatment plans, which will lead to the foundation of clinically relevant \( \text{EQD}_2 \) values. \( \text{EQD}_2 \)-based optimization is also effective in multi-centre trials, when the fractionation schedule is not fixed, but \( \text{EQD}_2 \) prescription and dose constraints are specified.

Finally, institute-specific and treatment-site specific protocols should be developed for IIP. With a protocol, manually executed by a user, fixed steps are followed to obtain a single or several treatment plan suggestions. The required level of automation is still to be determined. This will lead to less user-dependent and more reproducible treatment plans. Agreement between physicians on values and priorities for a set of distinct DVH parameters is desirable. Consensus on values of a prioritized set of DVH parameters will lead to standardized protocols for treatment planning.

Not much is known about the qualification of a ‘good’ plan. This is generally a subjective measure and its definition differs between physicians. More studies are needed correlating clinical results to dosimetry. Until then, in clinical practice, the choice between different treatment planning methods will be based on other metrics as well. These metrics include the duration of treatment planning and the ease of treatment planning, which is partly determined by the agreement between input parameters and resulting dose distribution.
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